Endocrine
https://doi.org/10.1007/s12020-020-02358-6

ORIGINAL ARTICLE

Entropy and uniformity as additional parameters to optimize the effectiveness of bone CT in the evaluation of acromegalic patients

Olga de Castro Dytz[1] · Pedro de Azevedo Berger[2,3] · Márcio Garrison Dytz[1] · Bernardo Alves Barbosa[1] · Armindo Jreige Júnior[1,2] · Neysa Aparecida Tinoco Reggatieri[4] · Arthur Disegna[1,2] · Wagner Diniz de Paula[4] · Luiz Augusto Casulari[1,2] · Luciana Ansaneli Naves[1,2]

Received: 23 December 2019 / Accepted: 18 May 2020

Abstract

Purpose Acromegaly is considered an important cause of secondary osteoporosis. However, studies on bone mineral density (BMD) have yielded conflicting results and there are few studies that evaluate an accurate imaging method for early diagnosis of osteoporosis in these patients. The objective of this study was to assess whether entropy and uniformity on computed tomography (CT) scans are useful parameters for optimization of assessment of bone fragility in patients with acromegaly.

Methods We included 34 patients and 36 controls matched for age and sex in a cross-sectional study. Patients and controls underwent CT scan of the lumbosacral spine, dual-energy x-ray absorptiometry (DXA) and blood tests. A software was developed to calculate the entropy and uniformity by a region of interest (ROI) of the trabecular bone of the first lumbar vertebra (L1).

Results The acromegalic group presented higher mean bone entropy (6.87 ± 0.98 vs. 6.03 ± 1.68, $p = 0.013$) and lower mean bone uniformity (0.035 ± 0.704 vs. 0.113 ± 0.205, $p = 0.035$) than control group. Analyzing only acromegalics, mean bone entropy was higher and bone uniformity was lower in patients with hypogonadism than patients without hypogonadism (7.28 ± 0.36 vs. 6.74 ± 1.08, $p = 0.038$ and 0.008 ± 0.002 vs. 0.043 ± 0.079, $p = 0.031$) respectively. Patients with acromegaly presented higher BMD and *Z*-score in the femoral neck than control group (1.156 ± 0.108 vs. 0.925 ± 0.326 g/cm^2, $p = 0.043$ and 0.6 ± 0.6 vs. -0.05 ± 0.8, $p = 0.041$, respectively). Entropy was negatively correlated with *T*-score of the lumbar spine ($r_p = -0.357$, $p = 0.033$) in control group and uniformity was positively correlated with *T*-score of the lumbar spine, neck, and total hip, respectively ($r_p = 0.371$, $p = 0.031$; $r_p = 0.348$, $p = 0.043$ and $r_p = 0.341$, $p = 0.049$) in acromegalic group.

Conclusions The study identified that entropy and uniformity are a relevant parameters data in bone fragility assessment in acromegalic patients.

Keywords Acromegaly · Osteoporosis · Entropy · Uniformity

Introduction

Acromegaly is a chronic disease of indolent slow evolution that is generally caused by the excessive secretion of GH from a pituitary tumor [1]. Among the effects of GH and subsequently of IGF-1 in several organs and systems, the effects on bone and thickening of periarticular fibrous tissues are highlighted, causing arthropathy, pain, edema, and difficulty in mobility [2]. Acromegalic patients exhibit increased bone turnover caused by the direct stimulation of GH or by IGF-1 and this condition is considered one of the important causes of secondary osteoporosis [3].

✉ Olga de Castro Dytz
olgadytz@gmail.com

1 Department of Endocrinology, University Hospital of Brasilia, University of Brasilia, Brasilia, Brazil

2 Faculty of Medicine, University of Brasilia, Brasilia, Brazil

3 Department of Computer Science, University of Brasilia, Brasilia, Brazil

4 Department of Radiology, University Hospital of Brasilia, University of Brasilia, Brasilia, Brazil

Published online: 10 June 2020

Dual-energy x-ray absorptiometry (DXA) is currently used to diagnose and follow the treatment of osteoporosis in adults [4]. However, DXA has been shown in several studies not be effective in diagnosing osteoporosis in acromegalic patients because it is a two-dimensional examination and does not quantify some of the factors that contribute to bone strength, such as morphology and microarchitecture [5]. Several studies have shown that some factors, such as hypogonadism and disease activity, interfere in bone mineral density (BMD) [6]. Vertebral fractures have been reported to occur in acromegaly patients independently of BMD [7].

Since DXA has limitations in the assessment of fracture risk in acromegalic patients, thoracic and lumbar x-ray may be useful for diagnosis of spinal deformities and fracture, particularly in symptomatic patients [8]. Patients with acromegaly should be evaluated for osteoporosis risk factors including vitamin D deficiency, inadequate calcium intake, serum calcium, and PTH to assess hyperparathyroidism, glucocorticoid over-replacement, and hypogonadism [7, 8].

Computed tomography (CT) images of the lumbar spine can clearly distinguish the trabecular and cortical bones [9] but are not able to specify further details of the bone microarchitecture. High-resolution peripheral quantitative computed tomography (HR-pQCT) equipment and trabecular bone score (TBS) software are very efficient methods to assess the bone microarchitecture but few services offer them because of their high cost [10].

The major challenge is to increase the diagnostic accuracy of acromegalic bone structure evaluated in conventional CT, method available in most healthcare services. Entropy and uniformity represent additional image parameters that can quantify homogeneity, brightness, and features that are observed visually as an image texture. Although little used in clinical radiology, the term entropy has been widely applied in computer theory as a useful measure of the elements of an image [11].

This is the first study to analyze bone entropy and uniformity in CT images in bone evaluation in acromegalic patients. The aim of the present study is to compare bone entropy and uniformity evaluated by CT of the lumbar spine and DXA results in a cohort of acromegalic patients and healthy controls. Secondary objectives are to compare the results among acromegalic with gonadal function, diagnosis of diabetes and disease activity, and correlate the entropy and uniformity of all participants and DXA results.

Method

Study population

This cross-sectional study was approved (protocol number 1.178.769) by the Ethical Committee of the Faculty of Health Sciences of the University of Brasilia in Brazil. The written informed consent form was obtained from each participant.

A total of 34 acromegalic patients (ACRO) from the same center and 36 age and gender-matched volunteers (control) were enrolled from August 2015 to November 2017.

ACRO were recruited from the Neuroendocrine Service of the University Hospital of Brasilia and controls were recruited among the hospital staff and volunteers. The eligible criteria were: clinical, hormonal diagnosis of acromegaly (glucose tolerance test with nadir GH > 0.4 ng/mL and age-increased IGF-1) [12], age >20 years at diagnosis and detectable pituitary tumor by nuclear magnetic resonance. The control group must have normal GH and IGF-1 concentrations for age. The exclusion criteria for both groups were: alcoholism, chronic gastrointestinal or inflammatory rheumatologic diseases, hemochromatosis and homocystinuria, renal or hepatic failure, use of drugs that interfere with bone metabolism, primary or secondary hyperparathyroidism due to vitamin D deficiency and pregnancy.

Clinical and biochemical parameters

Through anamnesis, physical examination and filling of specific form, the data of the research participants were collected, as well as blood samples after adequate fasting. The body mass index (BMI) was calculated using the weight to height ratio and is expressed in kilograms per square meter. The serum levels of GH, IGF-1, PTH, Ca, P, albumin, magnesium, 25(OH)D, AST, ALP, alkaline phosphatase, glucose, TSH, and free T4 were measured by chemiluminescence. Active disease was considered as age-increased IGF-1 or non-suppressibility of GH on glucose oral test. Primary hypogonadism was defined in women as postmenopause or at least 12 months of amenorrhea or low estradiol levels, and in men as the presence of signs and symptoms associated with a low serum testosterone. Secondary hypogonadism was defined as low gonadotrophins and sex steroid levels. The considered ranges of 25(OH)D concentrations indicating vitamin D deficiency [<20 ng/ml (<50 nmol/l)], suboptimal status [20–30 ng/ml (50–75 nmol/l)], optimal status [30–50 ng/ml (75–125 nmol/l)] [13].

Image analysis

All study participants performed lumbar spine, femoral neck, total femur, and radius 33% DXA using the GE Lunar Prodigy Advance (GE Healthcare Madison, WI, USA). Only one examiner did all the processing and reading of the exams. BMD was measured in the lumbar spine, femoral neck, total femur, and radius 33% and expressed in absolute

values (grams per square centimeter) and SD from peak bone mass (*T*-score) and from the expected BMD for the age matched population (*Z*-score). The reference group for the calculation of the *T*-score was from the National Health and Nutrition Examination Survey III (NHANES III) database. The coefficients of variability of BMD measures at our institution are 1.5% in the lumbar spine and 2.3% in the femoral neck.

Using the criteria of the International Society of Clinical Densitometry, the analysis of bone densitometry in men between 18 and 50 years of age and in women between the ages of 18 and menopause was done through the *Z*-score. The terminology used in cases of *Z*-score ≤ −2.0 was "a lower-than-expected BMD based on age". In the other individuals, the *T*-score was used and the classification was normal (0 to −1.0), osteopenia (<−1.0 to >−2.5) and osteoporosis (≤−2.5) [14].

Patients and controls underwent a CT scan of the lumbosacral spine (quantitative method) with irradiation of the L1–L5 vertebrae without contrast. The 32-channel General Electric LightSpeed VCT® was calibrated daily to ensure the accuracy of measured attenuation values.

Bone entropy and uniformity measurement

For bone entropy and uniformity measurement, new software was developed. The computer program was developed at the Computer Science Department of the University of Brasilia. MATLAB (Mathworks Inc, Natick, USA) was used for software development. This program provided visual information of soft tissue and bone on scales of shades of gray ranging from 0 (black) to 300 (white).

The segmentation of the bone tissue was performed automatically drawn within the limits of the first lumbar vertebra (L1). A region of interest (ROI) was selected at the center of the vertebral body of L1, corresponding to the trabecular portion of the bone. It was avoided to select areas close to structures that could distort the measures analyzed, such as areas near the posterior venous plexus, areas with focal heterogeneity, fractured vertebrae, and artefacts related to the image (Fig. 1).

For each ROI, the parameters bone entropy, a measure indicating both intensity and lack of homogeneity (irregularity), and bone uniformity, indicating how close the image is to a uniform distribution of shades of gray, were determined (Fig. 1). These parameters are defined mathematically below [15–17].

R = region of interest of image $I(x, y)$

N = number of total pixels in the region of interest R

$p(\mathrm{i})$ = probability of the occurrence of the gray level i

$$\text{Entropy}\,(E) = -\sum p(\mathrm{i})\log_2 p(i)\,,$$

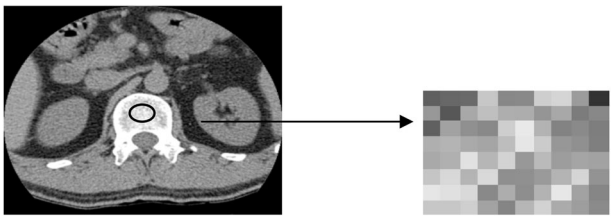

Fig. 1 The entropy and uniformity are calculated by a computer software from a section of L1 trabecular bone on CT scan

$$\text{Uniformity}\,(U) = \sum [p(i)]^2\,.$$

Entropy and uniformity are ratios and we calculate the summation of probability of gray scale of each pixel of the image of the trabecular portion of L1 extracted from a CT image, expressed as absolute values. There is no normal reference range.

Statistical analysis

SPSS 20.0 was used for statistical analysis. A $p < 0.05$ was considered statistically significant. Continuous variables were expressed as mean ± standard deviations and median and the categorical variable was expressed as percentages. For continuous variables, the normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Student's *t* test or Mann–Whitney *U* test was selected to compare variables between two groups with a normal or non-normal distribution, respectively. Proportions were compared by Chi-squared or Fisher's exact test. Correlations between two continuous variables were investigated by Pearson's (r_p) or Spearman's correlation coefficient (r_s). Stratified analysis was used to evaluate the influence of confounding variable on the results.

Results

Cohort

The findings from the clinical and biochemical analyses for all 70 enrolled subjects (34 ACRO and 36 controls) are summarized in Table 1. The ACRO and control group were similar in terms of gender and age. ACRO group presented higher BMI and higher frequency of smoking ($p = 0.008$), sedentary lifestyle ($p < 0.001$), diabetes ($p = 0.002$), arthralgia ($p < 0.001$), and family history of osteoporosis ($p = 0.002$). Vitamin D deficiency was observed in 13% of acromegalic patients.

In the ACRO group, 59% of patients had the disease controlled, with IGF-1 in the normal range for age.

Table 1 Clinical and biochemical characteristics of ACRO and control groups

Variables	ACRO group	($n = 34$)			Control group	($n = 36$)			
	Mean ± SD	Median	Interquartile range	*n* (%)	Mean ± SD	Median	Interquartile range	*n* (%)	*p*
Age (years)	50.4 ± 11.7	51	42–62.5		52.0 ± 12.1	52.5	43.2–61.7		0.989
Female *n* (%)				16 (47.1)				17 (47.2)	0.845
Male *n* (%)				18 (52.9)				19 (52.8)	0.845
BMI (kg/m²)	30.1 ± 4.3	30.1	27–34		25.6 ± 13.6	27.3	22.1–29.9		0.044
Diabetes *n* (%)				7 (20.6)				1 (2.8)	0.002
Arthralgia *n* (%)				18 (52.9)				8 (22.2)	<0.001
Smoking *n* (%)				7 (20.6)				8 (22.2)	0.008
Sedentary lifestyle *n* (%)				23 (67.6)				7 (19.4)	<0.001
Osteoporosis in family *n* (%)				3 (8.8)				9 (25)	0.002
Hypogonadism *n* (%)				8 (23.5)				5 (13.9)	0.007
Entropy	6.92 ± 0.53	6.95			7.30 ± 0.61	7.17			<0.001
Uniformity	0.0096 ± 0.0038	0.0087			0.1102 ± 0.1580	0.0095			<0.001
PTH (pg/mL)	42.1 ± 22.6	34.6	25–55.8		44.6 ± 20.2	40.3	33.9–51.6		0.678
25-hydroxyvitamin D (ng/mL)	25 ± 9	26.3	17.9–31.6		28 ± 12	30	23.7–35		0.390
Calcium (mg/dL)	9.3 ± 0.5	9.2	9.1–9.7		9.4 ± 0.4	9.4	9.1–9.7		0.635
Magnesium (mg/dL)	2.05 ± 0.5	2.0	1.8–2.3		2.01 ± 0.1	2.1	2.0–2.2		0.613
Alcaline phosphatase (U/L)	69 ± 26	65	51–88		71 ± 27	75	56.7–85.7		0.826
Albumin (g/dL)	4.1 ± 0.3	4.2	4.1–4.4		4.2 ± 0.2	4.5	4.3–4.7		0.183
Glucose (mg/dL)	105 ± 35	98	89.5–10.5		97 ± 12	95.5	90–102.5		0.306
HbA1c (%)	6.2 ± 1.1	6.0	5.4–6.4		5.2 ± 1.5	5.4	5.2–5.9		0.022
AST (U/L)	21 ± 6	21	17–24		24 ± 10	20	18–26		0.220
ALT (U/L)	23 ± 11	22	17–27		29 ± 18	21	16–47		0.184

BMI body mass index, *PTH* parathyroid hormone, *HbA1c* glycosylated hemoglobin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Table 2 Treatment and comorbidities in acromegalics patients ($n = 34$)

Variables	
Time since diagnosis (years)	12 ± 7
Non controlled disease (%)	41
Comorbidities	
Adrenal insufficiency (%)	8.8
Hypogonadism (%)	23.5
Hypothyroidism (%)	
Treatment	12.5
Neurosurgery alone (%)	14
Adjuvant therapy	76.4
Radiotherapy (%)	8.8
Somatostatin analog (%)	23.5
Somatostatin analog + cabergoline (%)	44.1
Primary somatostatin analog treatment (%)	8.8

Neurosurgery was performed in 91% of patients and 76% of them were submitted to adjuvant therapy. Hypogonadism was the most prevalent endocrine comorbidity (Table 2) affecting seven women (87.5 %) and one man (12.5%). Fourteen percent were doing hormone replacement.

Bone densitometry

The results of DXA showed that 23 (67%) ACRO group had normal BMD, 9 (26%) presented osteopenia and 2 patients had a "lower-than-expected BMD based on age". In the control group, 30.5% of subjects had osteopenia. The BMD and the *Z*-score in the femoral neck, analyzed by DXA, were higher in male patients lower than 50 years and premenopausal women (1.156 ± 0.108 vs. 0.925 ± 0.326 g/cm^2, $p = 0.043$ vs. 0.6 ± 0.6 vs. -0.05 ± 0.8, $p = 0.041$, respectively).

Computed tomography (CT)

In lumbosacral image evaluation, the most frequent anatomic alterations were anterolateral marginal osteophytes, intervertebral disc bulges and accentuation of sacrococcygeal angulation, even in younger patients. Lumbar interapophyseal arthritis, spondylolisthesis, ankylosis, and scoliosis were observed only in ACRO group. No vertebral fracture was observed in both groups. The structural changes detected in the lumbosacral spine are described in Table 3.

Entropy and uniformity studies

Entropy and uniformity were calculated at the ROI, corresponding to trabecular bone in the center of the vertebral body of L1.The mean bone entropy was higher in the ACRO group than in the control group (6.87 ± 0.98 vs. 6.03 ± 1.68, $p = 0.013$), (Fig. 2a). Uniformity was lower in the ACRO group than in the control group (0.035 ± 0.704 vs. 0.113 ± 0.205, $p = 0.035$) (Fig. 2b).

Table 3 Frequency of bone abnormalities in the lumbar spine of the participants

Lumbar spine abnormalities	ACRO (%)	Control (%)
Anterolateral marginal osteophytes	68	58
Intervertebral disc abutments	53	76
Accentuation of sacrococcygeal angulation	37	0
Lordosis lumbar	31	11
Interfacial arthritis	28	29
Lumbar interapophyseal arthrosis	21	0
Lumbar disc herniation	18	5
Bilateral isthmic spondylolisthesis	9	0
Ankylosis of sacroiliac joint	9	0
Scoliosis	6	0
Anterolisthesis	6	5
Thorny arthritis	6	0
Retrolisthesis	3	0
Vertebral hemangioma	3	0
Tarlov cysts	3	0

Evaluation of the entropy and uniformity among several conditions found in ACRO group are shown on Table 4. Analyzing only acromegalics, mean bone entropy was higher ($p = 0.038$) and bone uniformity was lower ($p = 0.031$) in patients with hypogonadism than patients without hypogonadism.

There was no difference between entropy and uniformity related to disease activity. The mean of entropy and uniformity was also not different between the ACRO group with and without type 2 diabetes mellitus ($p = 0.99$ and 0.92, respectively) (Table 4).

The Fig. 3 shows the CT images of the patient and controls with greater entropy and greater uniformity.

Uniformity was positively correlated with *T*-score of the lumbar spine, neck and total hip, respectively ($r_p = 0.371$, $p = 0.031$; $r_p = 0.348$, $p = 0.043$, and $r_p = 0.341$, $p = 0.049$) in ACRO group. Entropy was negatively correlated with *T*-score of the lumbar spine ($r = -0.357$, $p = 0.033$) in control group. Only variables with statistically significant correlation are present (variables with $p > 0.005$ are not reported).

Discussion

Patients with acromegaly have an increased risk of morphometric vertebral fractures. This seems to correlate with acromegaly activity and its duration, but it persists after

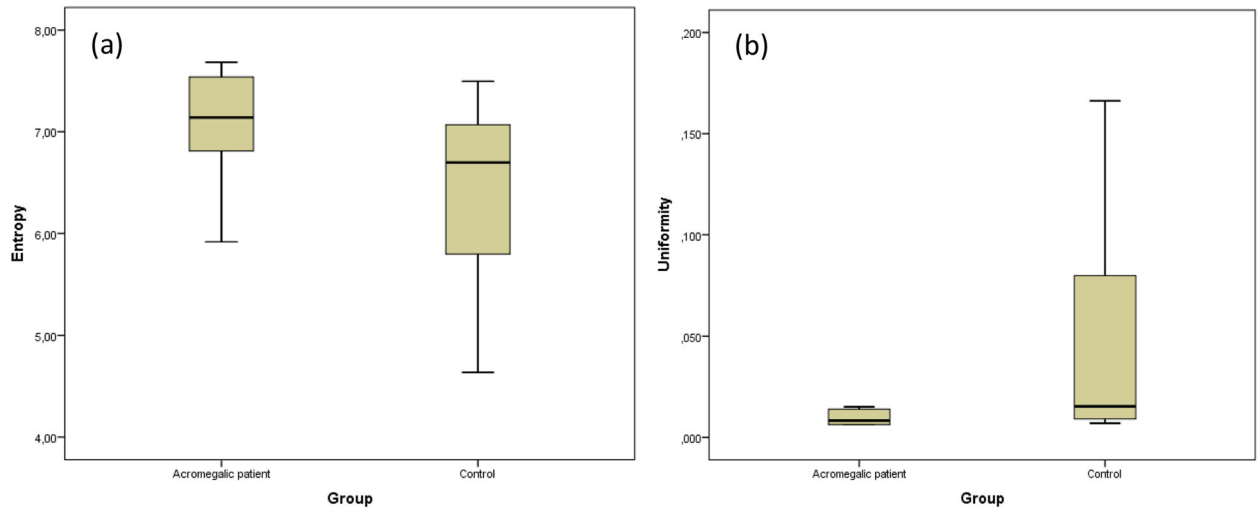

Fig. 2 Analysis of entropy (**a**) and uniformity (**b**) in ACRO and control group

Table 4 Entropy and uniformity evaluated in ACRO according to disease control, diabetes, and gonadal function

Variables	Disease control			Comorbidities					
	Active ($n = 14$)	Controlled ($n = 20$)	p	Hypogonadism ($n = 8$)	Eugonadism ($n = 26$)	p	Diabetes ($n = 7$)	Normoglycemia ($n = 27$)	p
Entropy	6.69 ± 0.94	6.99 ± 1.01	0.378	7.28 ± 0.36	6.74 ± 1.08	0.038	6.87 ± 1.00	6.87 ± 0.99	0.990
Uniformity	0.041 ± 0.067	0.031 ± 0.074	0.699	0.008 ± 0.002	0.043 ± 0.079	0.031	0.033 ± 0.067	0.035 ± 0.072	0.929

Data expressed in Mean ± SD

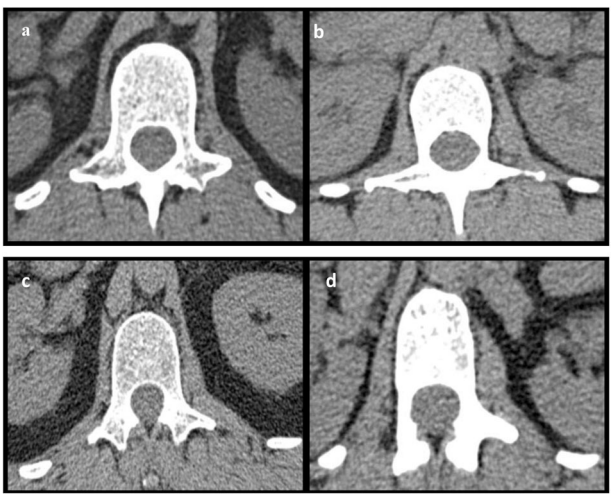

Fig. 3 The images show a CT images, axial cut in L1 vertebra. Image **a** represents the patient with greater entropy. Image **b** represents the patient with greater uniformity. Image **c** represents the control with greater entropy. Image **d** represents the control with greater uniformity

biochemical control achieved. The presence of hypogonadism, diabetes mellitus and over-replacement with glucocorticoids has extra harmful effects. BMD can be normal, increased, or decreased, and is usually discordant with occurrence of fractures. However, a decrease in the hip BMD during follow-up has been associated with development of new vertebral fractures [7, 18].

This is the first study to use entropy and uniformity in bone tissue and as additional parameters to increase the effectiveness of the analysis of bone tissue images extracted from trabecular portion lumbosacral spine (L1) CT in ACRO. Entropy and uniformity represent the values of an image that can quantify the image's homogeneity, brightness and texture. Until recently, entropy and uniformity were less known in clinical radiology, although the term entropy is applied in computer theory as a useful measure of the elements of an image. However, several clinical studies have shown promising results as a useful tool for assessing bone and soft tissues. In 2010, Ganeshan et al. demonstrated that entropy and uniformity were more sensitive parameters than the attenuation and perfusion coefficient to detect changes in metastatic liver tumors in patients undergoing contrast-enhanced CT for follow-up after colorectal cancer resection [15]. Fujimoto et al. compare entropy, extracted from magnetic resonance imaging of a region of the right hepatic lobe, of patients with hepatitis C, and liver damage, with the entropy of a group of individuals with normal liver function. The histopathological scale of the degree of fibrosis and liver inflammatory activity METAVIR was used and observed that the higher the stage of fibrosis and

liver inflammatory activity, the greater the entropy ($p = 0.001$, for all comparisons) concluding that entropy in patients with chronic hepatitis C it was a useful tool in predict the stage of liver fibrosis and inflammation [19]. Kolacinski et al. evaluated the change in entropy during the bone healing process after apicectomy, dental surgery to remove the tip of the tooth root, performed when conventional root canal therapy fails. One hundred twenty dental radiographs were taken, immediately after the surgical procedure (T0) and also 3 months (T1) and 12 months (T2) postoperatively. The entropy value of a region of normal trabecular bone, far from the region with bone loss, was also extracted to serve as a "reference value for normal bone". Higher entropy was observed at times T0, which decreased in times T1 and T2 until reaching "normal bone reference values", which was observed in T2, showing that entropy can be useful for assessing the bone regeneration process [20]. Dercle et al. also demonstrated in their study that entropy is a promising quantitative biomarker for characterizing the image phenotype of multiple primitive neoplasms (occurrence in the same individual of two or more malignant neoplasms involving one or more organs). When analyzing 525 patients with different types of tumors, the most frequent being lung, head and neck, colorectal and urothelium, it was observed that entropy was positively associated with gene expression, tumor metabolism and stage, prognosis and response to treatment, in addition to positively correlate with the presence of metastases (when present and the greater the focus of metastases, the greater the entropy) [21]. There are some benefits of assessing entropy and uniformity over other promising imaging methods in assessing bone microarchitecture [22].

Our study was transversal so we used results of entropy and uniformity of healthy age and gender-matched controls to compare with results obtained from ACRO group. When compared with the control group, patients with acromegaly presented higher entropy and lower uniformity. When we analyzed only the ACRO we observed that the hypogonadic patients present higher entropy and lower uniformity. We did not find difference between entropy and uniformity considering the presence of diabetes, disease control, and time of disease. Bonadonna et al. studied the frequency of radiological vertebral fractures in a cohort of postmenopausal women with active or controlled acromegaly and observed an increased risk of fracture in those with active disease (high GH and IGF-1) [23]. Mazziotti et al., in 2008 found a more vertebral fractures in acromegalic men compared with healthy individuals with no significant difference in BMD in patients with active disease and without interference with gonadal function [24].

Scillitani et al. evaluated BMD in 152 ACRO of both sexes with varying disease activity and gonadal status and evaluated the effect of GH excess on bone at different sites in relation to gonadal status, disease activity and gender and observed that the anabolic effect of GH excess on bone in ACRO is gender-independent ($p = \text{NS}$), higher at the spine only in eugonadal regardless of disease activity (active: -0.64 ± 0.35, $p < 0.05$; controlled: -1.05 ± 0.36, $p < 0.01$), lower in hypogonadal ones (active: -0.64 ± 0.35, $p < 0.05$; controlled: -1.05 ± 0.36, $p < 0.01$) and evident at femoral neck only in the presence of active disease regardless of gonadal status [25]. Zgliezynsk et al. conducted a study of 152 acromegalic patients with active disease and evaluated the influence of gonadal function on BMD in these patients. It was noticed that eugonadal acromegalics had higher *Z*-scores at all measured sites. Hypogonadal patients had significantly lower BMD at all sites, when compared with eugonadal acromegalics. Thirty five percent of hypogonadal subjects had *T*-score < -1 [26]. Using HR-pQCT in 82 patients with acromegaly, Madeira et al. have found a severe deterioration of trabecular bone microarchitecture that was correlated with patient's gonadal status rather than with the presence of type 2 diabetes or the activity of the disease. Therefore, a sub-analysis was performed on 45 eugonadal acromegalic patients compared with 45 healthy controls. The patients showed lower trabecular volumetric bone density, trabecular bone volume fraction and trabecular number than controls. Moreover they had higher trabecular separation and spacing than healthy subjects [27].

In the analysis of the parameters evaluated by DXA, differences in the mean BMD and *Z*-score in the femur (femoral neck and total femur) were showed between the groups. The group of patients with acromegaly with less than 50 years old or with premenopausal women presented higher BMD and higher *Z*-score in the femur compared with the control group. Probably, this is due to the many limitations of DXA, since it measures only the quantity of bone without evaluating the bone microarchitecture (quality) and include its 2D assessment of a BMD, which is influenced by the bone enlargement that which may be altered in acromegaly [24]. Moreover, DXA does not distinguish between the cortical and trabecular compartments, which may differentially contribute to bone strength and resistance to fracture [28]. However, 68% of patients showed osteophytes at lumbar spine potentially interfering the DXA results. Madeira et al. determined a significant prevalence of osteoporosis by bone densitometry (24.3%) and lower-than-expected BMD based on age in 24.4% of all the patients, suggesting a negative impact of the overall hormonal disturbance on the bone [28]. Eller-Vainiche et al., in a recent review, describe that the attempt to measure BMD by DXA has given inadequate results in acromegaly. Importantly, spine BMD is usually normal in this disease, while hip BMD may even be higher than normal [10]. We observed a negative correlation between entropy and *T*-score of the lumbar spine in control group and we did not observe any

correlation between entropy and DXA results in ACRO group. This finding may support the hypothesis that even DXA being the recommended exam for diagnosis of osteopenia and osteoporosis, it has limitations in specific populations such as acromegalic patients.

This data suggest that entropy and uniformity may be an additional tool in the evaluation of bone quality in acromegaly easy to reproduce and with relatively low cost, as an additional tool in centers that do not have the TBS and HR-pQCT. The present study is the first to be published using entropy and uniformity to investigate bone structure of ACRO. Some studies showed promising results with TBS and HR-pQCT that seem to be able to estimate bone quality. However a few services offer them because of their cost. Another aspect is that HR-pQCT only evaluates microstructure in the radius and tibia but not spine or hip (central skeleton).

A limitation of our study was the challenge of recruiting paired controls for risk factors for bone disease since diabetes, high BMI, hypogonadism are frequent comorbidities related to long exposure to GH hypersecretion or as a consequence of multiple treatment modalities in the acromegalic population. The cross-sectional study design prevented individual monitoring and changes in the DXA, entropy and uniformity parameters based on the treatment and period of disease control. More longitudinal and controlled studies are essential to evaluate our findings and to establish acromegaly in relation to worse bone quality and the occurrence of vertebral fracture.

Conclusion

The development of softwares including entropy and uniformity as parameters of CT lumbar spine analysis may represent an additional tool on conventional CT images in centers where HR-pQCT equipment and TBS software are not available. We observed in our study that entropy and uniformity has been shown a good marker of bone fragility in patients with acromegaly. Hypogonadism may represent an additional risk factor for bone fragility.

Our patients had a higher BMD than the control group by DXA.

The disease activity and type 2 diabetes mellitus did not significantly change the entropy and uniformity.

Acknowledgements The authors are grateful for the help of Dra. Jane Lynn Garrison Dytz and Edison Dytz who contributed significantly to this project.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consents Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of Ethics Committee of the Faculty of Health Sciences of the University of Brasilia (approval number 1.178.769) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. I.M. Holdaway, C. Rajasoorya, Epidemiology of acromegaly. Pituitary **2**, 29–34 (1999)
2. A. Giustina, G. Mazziotti, E. Canalis, Growth hormone, insulin-like growth factors, and the skeleton. Endocr. Rev. **29**, 535–559 (2008)
3. S. Ezzat, S. Melmed, D. Endres, D.R. Eyre, F.R. Singer, Biochemical assessment of bone formation and resorption in acromegaly. J. Clin. Endocrinol. Metab. **76**, 1452–1457 (1993)
4. P.G. Lacativa, M.L. de Farias, Office practice of osteoporosis evaluation. Arq. Bras. Endocrinol. Metab. **50**, 674–684 (2006)
5. E.M. Lewiecki, A.J. Laster, Clinical review: clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. J. Clin. Endocrinol. Metab. **91**, 4215–4222 (2006)
6. M. Bolanowski, J. Daroszewski, M. Medras, B. Zadrozna-Sliwka, Bone mineral density and turnover in patients with acromegaly in relation to sex, disease activity, and gonadal function. J. Bone Miner. Metab. **24**, 72–78 (2006)
7. M.J. Wassenaar, N.R. Biermasz, N.A. Hamdy, M.C. Zillikens, J. B. van Meurs, F. Rivadeneira, A. Hofman, A.G. Uitterlinden, M. P. Stokkel, F. Roelfsema, M. Kloppenburg, H.M. Kroon, J.A. Romijn, A.M. Pereira, High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly. Eur. J. Endocrinol. **164**, 475–83 (2011)
8. J.T. Schousboe, T. Vokes, S.B. Broy, L. Ferrar, F. McKiernan, C. Roux, N. Binkley, Vertebral fracture assessment: the 2007 ISCD official positions. J. Clin. Densitom. Off. J. Int. Soc. Clin. Densitom. **11**, 92–108 (2008)
9. P.J. Pickhardt, B.D. Pooler, T. Lauder, A.M. del Rio, R.J. Bruce, N. Binkley, Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. Ann. Intern. Med. **158**, 588–595 (2013)
10. C. Eller-Vainicher, A. Falchetti, L. Gennari, E. Cairoli, F. Bertoldo, F. Vescini, A. Scillitani, L. Chiodini, Evaluation of bone fragility in endocrine disorders. Imaging Endocr. Osteoporos. **180**, 213–232 (2019)
11. E.T. Jaynes, Information theory and statistical mechanics. Phys. Rev. J. Arch. **106**, 620–630 (1957)
12. S. Melmed, F.F. Casanueva, A. Klibanski, M.D. Bronstein, P. Chanson, S.W. Lamberts, C.J. Strasburger, J.A. Wass, A. Giustina, A consensus on the diagnosis and treatment of acromegaly complications. Pituitary **16**, 294–302 (2013)
13. J. Halupczok-Żyła, A. Jawiarczyk-Przybyłowska, M. Bolanowski, Patients with active acromegaly are at high risk of 25(OH) D deficiency. Front. Endocrinol. **2**, 89–95 (2015)
14. J.T. Schousboe, J.A. Shepherd, J.P. Bilezikian, S. Baim, Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J. Clin. Densitom. **16**, 455–466 (2013)

15. B. Ganeshan, K.A. Miles, R.C. Young, C.R. Chatwin, Hepatic entropy and uniformity: additional parameters that can potentially increase the effectiveness of contrast enhancement during abdominal CT. Clin. Radiol. **62**, 761–768 (2007)
16. R. M. Gray, Entropy and Information Theory. (Springer, 2011)
17. J. E. Shore, R. M. Gray, Minimum cross-entropy pattern classification and cluster analysis. IEEE Trans. Pattern Anal. Mach. Intell. **1**, 11–17 (1982)
18. T. Jalava, S. Sarna, L. Pylkkanen, B. Mawer, J.A. Kanis, P. Selby, M. Davies, J. Adams, R.M. Francis, J. Robinson, E. McCloskey, Association between vertebral fracture and increased mortality in osteoporotic patients. J. Bone Miner. Res. **18**, 1254–1260 (2003)
19. K. Fujimoto, T. Tonan, S. Azuma, M. Kage, T. Nakashima, J. Naofumi, H. Koji, K. Takumi, M. Sata, A. Qayyum, Evaluation of the mean and entropy of apparent diffusion coefficient values in chronic hepatitis C: correlation with pathologic fibrosis stage and inflammatory activity grade. Radiology **258**, 739–748 (2011)
20. M. Kolancinski, M. Kozakiewicz, A. Materka, Textual entropy as a potential feature for quantitative assessment of a jaw bone healing process. Arch. Med. Sci. **11**, 78–84 (2015)
21. L. Dercle, S. Ammari, M. Bateson, Limits of radiomic-based entropy as a surrogate of tumor heterogeneity: ROI-area, acquisition protocol and tissue site exert substantial influence. Sci. Rep. **7**, 1–10 (2017)
22. G.P. Lesse, W.D. Fraser, R. Farquharson, L. Hipkin, J.P. Vora, Gonadal status is an important determinant of bone density in acromegaly. Clin. Endocrinol. **48**, 59–65 (1998)
23. S. Bonadonna, G. Mazziotti, M. Nuzzo, A. Bianchi, A. Fusco, L. De Marinis, A. Giustina, Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. J. Bone Miner. Res. **20**, 1837–1844 (2005)
24. G. Mazziotti, A. Bianchi, S. Bonadonna, V. Cimino, I. Patelli, A. Fusco, A. Pontecorvi, L. De Marinis, A. Giustina, Prevalence of vertebral fractures in men with acromegaly. J. Clin. Endocrinol. Metab. **93**, 4649–4655 (2008)
25. A. Scillitani, C. Battista, I. Chiodini, V. Carnevale, S. Fusilli, E. Ciccarelli, M. Terzolo, G. Oppizzi, M. Arosio, M. Gasperi, G. Arnaldi, A. Colao, R. Baldelli, M.R. Ghiggi, D. Gaia, C. Di Somma, V. Trischitta, A. Liuzzi, Bone mineral density in acromegaly: the effect of gender, disease activity and gonadal status. Clin. Endocrinol. **58**, 725–731 (2003)
26. W. Zgliczynski, M. Kochman, W. Misiorowski, P. Zdunowski, In acromegaly, increased bone mineral density (BMD) is determined by GH-excess, gonadal function and gender. Neuro Endocrinol. Lett. **28**, 621–628 (2007)
27. M. Madeira, V.L. Neto, F.P.P. Neto, I.C.B.L. Lima, L.M.C.M. Mendonça, M.R. Gadelha, M.L.F. Farias, Acromegaly has a negative influence on trabecular bone, but not on cortical bone, as assessed by high-resolution peripheral quantitative computed tomography. J. Clin. Endocrinol. Metab. **98**, 1734–1741 (2013)
28. G. Mazziotti, M. Gola, M. Bianchi, T. Porcelli, A. Giampietro, V. Cimino, M. Doga, C. Gazzaruso, L. Marinis, A. Giustina, Influence of diabetes mellitus on vertebral fractures in men with acromegaly. Endocrine **40**, 102–108 (2011)